

FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning

Safety Announcement

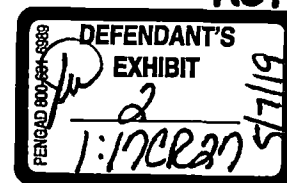
[8-31-2016] A U.S. Food and Drug Administration (FDA) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. Opioids are used to treat pain and cough; benzodiazepines are used to treat anxiety, insomnia, and seizures. In an effort to decrease the use of opioids and benzodiazepines, or opioids and other CNS depressants, together, we are adding *Boxed Warnings*, our strongest warnings, to the drug labeling of prescription opioid pain and prescription opioid cough medicines, and benzodiazepines.

Health care professionals should limit prescribing opioid pain medicines with benzodiazepines or other CNS depressants only to patients for whom alternative treatment options are inadequate. If these medicines are prescribed together, limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect. Warn patients and caregivers about the risks of slowed or difficult breathing and/or sedation, and the associated signs and symptoms. Avoid prescribing prescription opioid cough medicines for patients taking benzodiazepines or other CNS depressants, including alcohol.

Patients taking opioids with benzodiazepines, other CNS depressant medicines, or alcohol, and caregivers of these patients, should seek medical attention immediately if they or someone they are caring for experiences symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness. Unresponsiveness means that the person doesn't answer or react normally or you can't wake them up. Talk with your health care professional if you have questions or concerns about taking opioids or benzodiazepines (see List of Prescription Opioid Pain and Cough Medicines, and List of Benzodiazepines and Other CNS Depressants).

Opioids are a class of powerful narcotic medicines that are used to treat pain severe enough to warrant use of an opioid when other pain medicines cannot be taken or are not able to provide enough pain relief. They also have serious risks including misuse and abuse, addiction, overdose, and death. Opioids such as codeine and hydrocodone are also approved in combination with other medicines to reduce coughing. Benzodiazepines are

Refused



a class of medicines that are widely used to treat conditions including anxiety, insomnia, and seizures.

We conducted and reviewed several studies showing that serious risks are associated with the combined use of opioids and benzodiazepines, other drugs that depress the CNS, or alcohol (see Data Summary).¹⁻⁶ Based on these data, we are requiring several changes to reflect these risks in the opioid and benzodiazepine labeling, and new or revised patient Medication Guides. These changes include the new *Boxed Warnings* and revisions to the *Warnings and Precautions*, *Drug Interactions*, and *Patient Counseling Information* sections of the labeling.

We are continuing to evaluate the evidence regarding combined use of benzodiazepines or other CNS depressants with medication-assisted therapy (MAT) drugs used to treat opioid addiction and dependence. We are also evaluating whether labeling changes are needed for other CNS depressants, and will update the public when more information is available.

We urge patients and health care professionals to report side effects involving opioids, benzodiazepines, or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

List of Prescription Opioid Pain and Cough Medicines

Generic Name	Found in Brand Name(s)
alfentanil	Alfenta
buprenorphine	Belbuca, Buprenex, Butrans
butorphanol	No brand name currently marketed
codeine	Fioricet w/ codeine, Fiorinal w/ codeine, Soma Compound w/ codeine, Tylenol w/ codeine, Prometh VC w/ codeine (cough), Triacin-C (cough), Tuzistra-XR (cough)
dihydrocodeine	Synalgos-DC
fentanyl	Abstral, Actiq, Duragesic, Fentora, Ionsys, Lazanda, Sublimaze, Subsys
hydrocodone	Anexsia, Hysingla ER, Lortab, Norco, Reprexain, Vicodin, Vicoprofen, Zohydro ER, Flowtuss (cough), Hycofenix (cough), Obredon (cough), Rezira (cough), Tussicaps (cough), Tussigon (cough), Tussionex Pennkinetic (cough), Vituz (cough), Zutripro (cough)
hydromorphone	Dilaudid, Dilaudid-HP, Exalgo
meperidine	Demerol
methadone	Dolophine
morphine	Astramorph PF, Duramorph PF, Embeda, Infumorph, Kadian, Morphabond, MS

	Contin
oxycodone	Oxaydo, Oxycet, Oxycontin, Percocet, Percodan, Roxicet, Roxicodone, Xartemis XR
oxymorphone	Opana, Opana ER
pentazocine	Talwin
remifentanil	Ultiva
sufentanil	Sufenta
tapentadol	Nucynta, Nucynta ER
tramadol	Conzip, Ultracet, Ultram, Ultram ER

List of Benzodiazepines and Other CNS Depressants *

Generic Name	Brand Name(s)
Benzodiazepines	
alprazolam	Xanax, Xanax XR
chlordiazepoxide	Librium, Librax
clobazam	Onfi
clonazepam	Klonopin
clorazepate	Gen-Xene, Tranxene
diazepam	Diastat, Diastat Acudial, Valium
estazolam	No brand name currently marketed
flurazepam	No brand name currently marketed
lorazepam	Ativan
oxazepam	No brand name currently marketed
quazepam	Doral
temazepam	Restoril
triazolam	Halcion
Other Sleep Drugs and Tranquilizers	
butabarbital sodium	Butisol
eszopiclone	Lunesta
pentobarbital	Nembutal
ramelteon	Rozerem
secobarbital sodium	Seconal sodium
suvorexant	Belsomra
zaleplon	Sonata
zolpidem	Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist
Muscle Relaxants	
baclofen	Gablofen, Lioresal
carisoprodol	Soma, Soma Compound, Soma Compound w/ codeine
chlorzoxazone	No brand name currently marketed
cyclobenzaprine	Amrix
dantrolene	Dantrium, Revonto, Ryanodex

metaxalone	Skelaxin
methocarbamol	Robaxin, Robaxin-750
orphenadrine	No brand name currently marketed
tizanidine	Zanaflex
Antipsychotics	
aripiprazole	Abilify, Abilify Maintena, Aristada
asenapine	Saphris
cariprazine	Vraylar
chlorpromazine	No brand name currently marketed
clozapine	Clozaril, Fazaclo ODT, Versacloz
fluphenazine	No brand name currently marketed
haloperidol	Haldol
iloperidone	Fanapt
loxapine	Adasuve
lurasidone	Latuda
molindone	No brand name currently marketed
olanzapine	Symbyax, Zyprexa, Zyprexa Relprevv, Zyprexa Zydis
paliperidone	Invega, Invega Sustenna, Invega Trinza
perphenazine	No brand name currently marketed
pimavanserin	Nuplazid
quetiapine	Seroquel, Seroquel XR
risperidone	Risperdal, Risperdal Consta
thioridazine	No brand name currently marketed
thiothixene	Navane
trifluoperazine	No brand name currently marketed
ziprasidone	Geodon

*This is not a comprehensive list.

Facts about Opioids and Benzodiazepines

- Opioids are powerful prescription medicines that can help manage pain when other treatments and medicines cannot be taken or are not able to provide enough pain relief. Opioids such as codeine and hydrocodone are also available in combination with other medicines to treat coughing (see List of Prescription Opioid Pain and Cough Medicines).
- Common side effects of opioids include drowsiness, dizziness, nausea, vomiting, constipation, and slowed or difficult breathing. Opioids also carry serious risks, including misuse and abuse, addiction, overdose, and death.
- Benzodiazepines are a class of medicines that are widely used to treat conditions including anxiety, insomnia, and seizures (see List of Benzodiazepines and Other CNS Depressants).
- Common side effects of benzodiazepines include drowsiness, dizziness, weakness, and physical dependence.
- Both opioids and benzodiazepines depress the central nervous system (CNS).

- Both opioids and benzodiazepines are commonly prescribed drugs. In 2014 in the U.S., 81 million patients were dispensed an opioid, and 30 million patients were dispensed a benzodiazepine.¹

Additional Information for Patients

- Combining opioid pain or prescription opioid cough medicines with medicines called benzodiazepines, which are used for anxiety, insomnia, and seizures, can result in extreme sleepiness, slowed or difficult breathing, coma, or death. These serious side effects result because both opioids and benzodiazepines impact (depress) the central nervous system (CNS). The CNS controls most of the functions of the brain and body.
- These serious side effects can also occur when opioids are combined with other medicines that depress the CNS or alcohol (see List of Prescription Opioid Pain and Cough Medicines, and List of Benzodiazepines and Other CNS Depressants).
- Do not drink alcohol with any of these medicines. Alcohol also depresses the CNS and can increase the risk for these serious and life-threatening side effects.
- Given the serious side effects that may occur, if you are already taking both opioids and benzodiazepines or other medicines that depress the CNS, talk to your health care professional to see if continued combined use is needed.
- Do not take opioid pain medicines with benzodiazepines or other medicines that depress the CNS without discussing it with your health care professional. Do not take opioid cough medicines with benzodiazepines or other medicines that depress the CNS.
- Always inform all your health care professionals about all the medicines you are taking, including prescription and over-the-counter (OTC) medicines. It is helpful to keep a list of all your current medicines in your wallet or another location where it is easily retrieved. You can fill out and print a copy of My Medicine Record.
- If you are taking an opioid pain or cough medicine or a benzodiazepine and don't know if you are also receiving other medicines that may interact, contact your pharmacist or other health care professional.
- If you are taking both an opioid pain medicine and a benzodiazepine or other medicine that depresses the CNS, avoid driving or operating heavy machinery until you know how the medicines affect you.
- Opioids are powerful medicines that can help manage pain when other treatments and medicines are not able to provide enough pain relief. However, even when used properly, opioids also carry serious risks, and they can be misused and abused, causing addiction, overdose, and death. Benzodiazepines also carry the risk of dependence.
- It is important to lock up opioids and benzodiazepines and to dispose of them properly to keep them from being taken accidentally by children or falling into the wrong hands.
- Talk to your health care professional if you have any questions or concerns about opioids, benzodiazepines, or other medicines you are taking.
- Read the patient Medication Guide or patient information leaflet that comes with your filled prescription(s).

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The first study examined concomitant use patterns of opioid analgesics and benzodiazepines. Between 2002 and 2014, the annual number of patients dispensed an opioid analgesic increased 8 percent, from 75 million to 81 million, and the annual number of patients dispensed a benzodiazepine increased 31 percent, from 23 million to 30 million. During this period, the proportion of opioid analgesic recipients receiving an overlapping benzodiazepine prescription increased by 41 percent, which translates to an increase of more than 2.5 million opioid analgesic users receiving concomitant benzodiazepines in 2014, compared to 2002. The subgroups with the highest probability of receiving concomitant prescriptions were women, patients older than 65, and chronic users of opioid analgesics. However, in absolute numbers, concomitancy occurred most commonly in nonchronic opioid analgesic users, because they greatly outnumber chronic users.¹

The second study² used the Drug Abuse Warning Network (DAWN) to analyze ED visits due to nonmedical use of both prescription opioid analgesics and benzodiazepines, and the National Vital Statistics System Multiple Cause-of-Death file to analyze drug overdose deaths involving both prescription opioid analgesics and benzodiazepines. Between 2004 and 2011, the rate of nonmedical use-related ED visits involving both opioid analgesics and benzodiazepines increased from 11 to 34.2 per 100,000 population (p-trend <0.0001). During this same time period, drug overdose deaths, from taking prescribed or greater than prescribed doses and involving both opioid analgesics and benzodiazepines, increased from 0.6 to 1.7 per 100,000 (p-trend <0.0001). The proportion of prescription opioid analgesic overdose deaths in which benzodiazepines were also implicated increased from 18 percent to 31 percent during this time period (p-trend <0.0001).

Two additional studies published in the medical literature show more direct evidence of increased risk of adverse events occurring in patients dispensed both opioid analgesics and benzodiazepines. A prospective observational cohort study conducted in North Carolina found the rates of overdose death among patients co-dispensed opioid analgesics and benzodiazepines were 10 times higher (7.0 per 10,000 person-years; 95% confidence interval (CI): 6.3-7.8) than among patients dispensed opioid analgesics alone (0.7 per 10,000 person-years; 95% CI: 0.6-0.9).³ A case-cohort study examined the Veterans Health Administration data from 2004-2009 and found the risk of death from drug overdose increased among those with concomitant opioid analgesic and benzodiazepine prescriptions. Compared to patients taking opioid analgesics with no history of a benzodiazepine prescription, patients taking opioid analgesics with a history of a benzodiazepine prescription had an increased risk of fatal overdose (hazard ratio (HR)=2.33 (95% CI: 2.05-2.64)), and those with a current benzodiazepine prescription had a similarly increased risk (HR=3.86 (95% CI: 3.49-4.26)) for fatal overdose. In addition, the risk of drug overdose death increased as the daily benzodiazepine dose increased.⁴

Based on the trends of increased concomitant use of opioid analgesics and benzodiazepines as well as increased harms associated with concomitant use described in

these four studies, we are requiring a new *Boxed Warning* to be added to the labeling of opioid analgesic and opioid cough medications and benzodiazepines. Related revisions will also be made to the *Warnings and Precautions*, *Drug Interactions*, and *Patient Counseling Information* sections of the labeling.

Concomitant use of opioids and other central nervous system (CNS) depressants

Recent studies in the literature show that concomitant use of opioid analgesics and CNS depressants other than benzodiazepines, including alcohol, is also associated with serious adverse events. One study reported that opioid analgesics contributed to 77 percent of deaths where benzodiazepines were determined to be a cause of death, and benzodiazepines contributed to 30 percent of deaths where opioid analgesics were determined to be a cause of death. This study also analyzed the involvement of other CNS depressants (including barbiturates, antipsychotic and neuroleptic drugs, antiepileptic and antiparkinsonian drugs, anesthetics, autonomic nervous system drugs, and muscle relaxants) in these deaths and found that these CNS depressants were contributory to death in many cases where opioid analgesics were also implicated.⁵ A second study analyzed 2010 DAWN data and found that alcohol was involved in 18.5 percent of opioid analgesic abuse-related ED visits and 22.1 percent of opioid analgesic-related deaths.⁶

All of the studies were based on opioid analgesics; however, because of similar pharmacologic properties, it is reasonable to expect similar risks with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol. Based on these studies, the *Boxed Warning* for opioid analgesics and opioid cough medications will also highlight the risk of concomitant use with other CNS depressants.

Due to the unique medical needs and benefit/risk considerations for patients taking medication-assisted therapy (MAT) to treat opioid addiction and dependence, we are continuing to examine available evidence regarding the concomitant use of benzodiazepines and MAT drugs.

References

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Related Information

Opioid Medications

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines